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EMERGING ROLE OF NANOEMULGEL IN NOVEL DRUG DELIVERY SYSTEM

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Abstract: A Nanoemul gel is a topical gel that contains a nanoemulsion dispersed within a gel matrix. The nanoemulsion is typically prepared using high shear mixing techniques and contains droplets of an oil phase dispersed in an aqueous phase stabilized by surfactants or stabilizers [1].The resulting Nanoemul gel has several advantages over traditional emulsion-based gels, including improved stability, enhanced drug penetration, and increased bioavailability. Nanoemul gels have been studied for their potential in dermatology and drug delivery applications, showing promising results in reducing acne lesions and improving skin appearance, as well as enhancing drug delivery and reducing inflammation. Further research is needed to optimize the formulation and assess the safety and effectiveness of Nanoemul gels for different applications. Nanoemulgel consist two different systems in which drug containing nanoemulsion is incorporated into a gel base [2]. The fusion of these two systems makes this formulation advantageous in several ways. Lipophilic drugs can be easily incorporated and the skin permeability of the incorporated drugs can be enhanced in several folds due to the finely distributed oil droplets in gel phase. Simultaneously, it can be targeted more specifically to the site of action and can avoid first pass metabolism and relieve the user from gastric/systemic incompatibilities. The nanoemulgel drug delivery system is a formulation related intervention to improve drug absorption and therapeutic profile of lipophilic drugs. An increasing trend in nanoemulgel use in recent years has been noticed because of the better acceptability of the preparation to the patients due to their non-greasy, convenience spreadiability, and easy applicability and good therapeutic and safety profile. Despite having few limitations, nanoemulgel formulation can be considered as potential and promising candidates for topical delivery of lipophilic drugs in the future [3].

Keywords: Nanoemulgel; Topical Formulation; Drug Delivery through skin.

1. INTRODUCTION

A type of structural fluid known as a nanoemulsion gel combines the characteristics of nanoemulsions and gels. Nanoemulsions are clear or translucent, thermodynamically stable dispersions of oil and water, with typical droplet sizes ranging from 20 to 200 nm. Due to their large surface area and potential to improve drug solubility , bioavailability, and targeted distribution ,they are frequently used as drug delivery systems.

Gels, on the other hand, are semisolid systems made up of a three-dimensional network of crosslinked polymer chains, and they can offer advantageous qualities like increased adhesion, extended residence time, and improved skin penetration.

Nanoemulsions gels can offer a special set of benefits in drug delivery by combining these two systems, including increased stability, controlled release, and improved skin permeability. Nanoemulsions are a type of emulsion that has droplets in nanometer range. They are considered to have better stability and bioavailability than traditional emulsions due to their small droplet size. Nanoemulsions are commonly used in various industries, including the food, cosmetic, and pharmaceutical industries.

Nanoemulgels are topical gels contain nanoemulsions. They are commonly used in dermatology for the treatment of skin conditions such as eczema, relief, pscoriasis and acne. They can also be used to deliver medications for pain relief, anti-inflammatory agents, and anti-infective agents. Nanogels are nanoparticles - based hydrogels that have been studied for their potential in drug delivery, tissue engineering and other biomedical applications. They are commonly used due to their biocompatibility , biodegradability and high drug loading capacity[4].

2.NANOEMULSION:

Nano-emulsions are an isotropic biphasic mixture consisting of two portions: water and oil, where one phase is dispersed in the other as nanosized droplets [5].

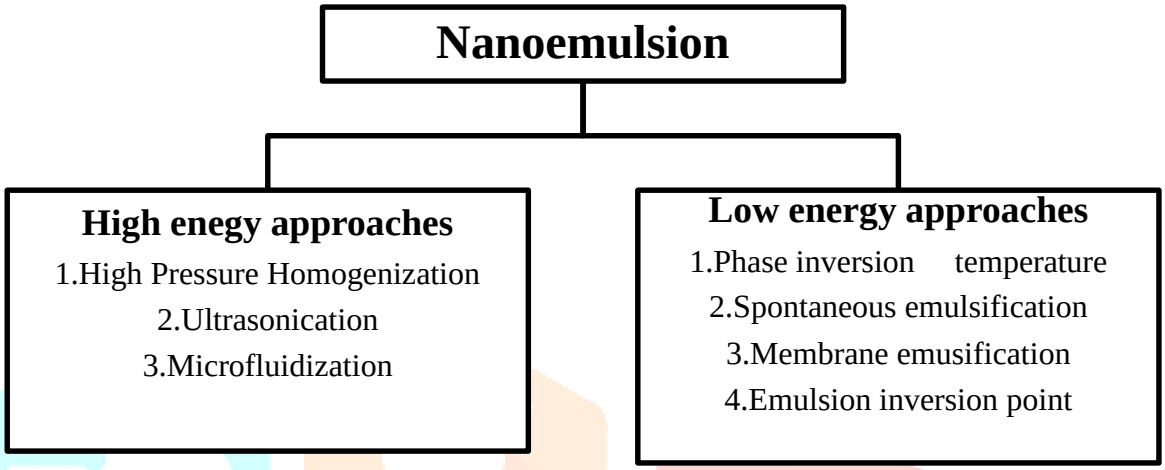

Fig1:Schematic representation of method of preparation in nanoemulsion.

Table 1: Currently marketed pharmaceutical nanoemulsion products

Trade Name	Drug	Dosage Form Route Of Administration	Indication
Diprivan	Propofol	Intravenous	Anaesthetic
Limethason	Dexamethasone	Intravenous,Intraveteral,Eye Drop	Steroid
Ropion	Flurbiprofen Axetil	Intravenous	Nonsteroidal analgesic
Troypofol	Propofol	Intravenous	anaesthetic
Liple	Alprostadil Palmitate	Intravenous	Vasodilator platelet inhibitor
Vitalipid	Vitamin A,D,E,K	Parentral	Parentral nutrition

3.NANOEMULGEL:

Nano-emulgel is formed by incorporating the nano-emulsion into a hydrogel matrix, which reduces the thermodynamic instability of the emulsion [6].

Table 2:Currently Marketed Pharmaceutical Nanoemulgel Product

Trade Name	Drug	Dosage Form Route Of Administration	Indication
Voltaren	Diclofenac Diethylamine	Topical	Inflammation/Pain
Isofen	Ibuprofen	Topical	Antiinflammatory
Miconaz-H	Miconazole nitrate	Intraveteral	Vaginal Infection
Diclomax	Diclofenac diethylamine	Topical	Antiinflammatory
Benzolait	Benzoyl Peroxide And Biguanide	Topical	Pain Releiver

Micnaz-H	Miconazole Nitrate And Hydrocortisone	Topical	Antifungal
Dermafeet	Urea	Topical	Antifungal
Adwiflam	Diclofenac Diethylamine	Topical	Antiinflammatory

3.1.Components Of Nanoemulgel :

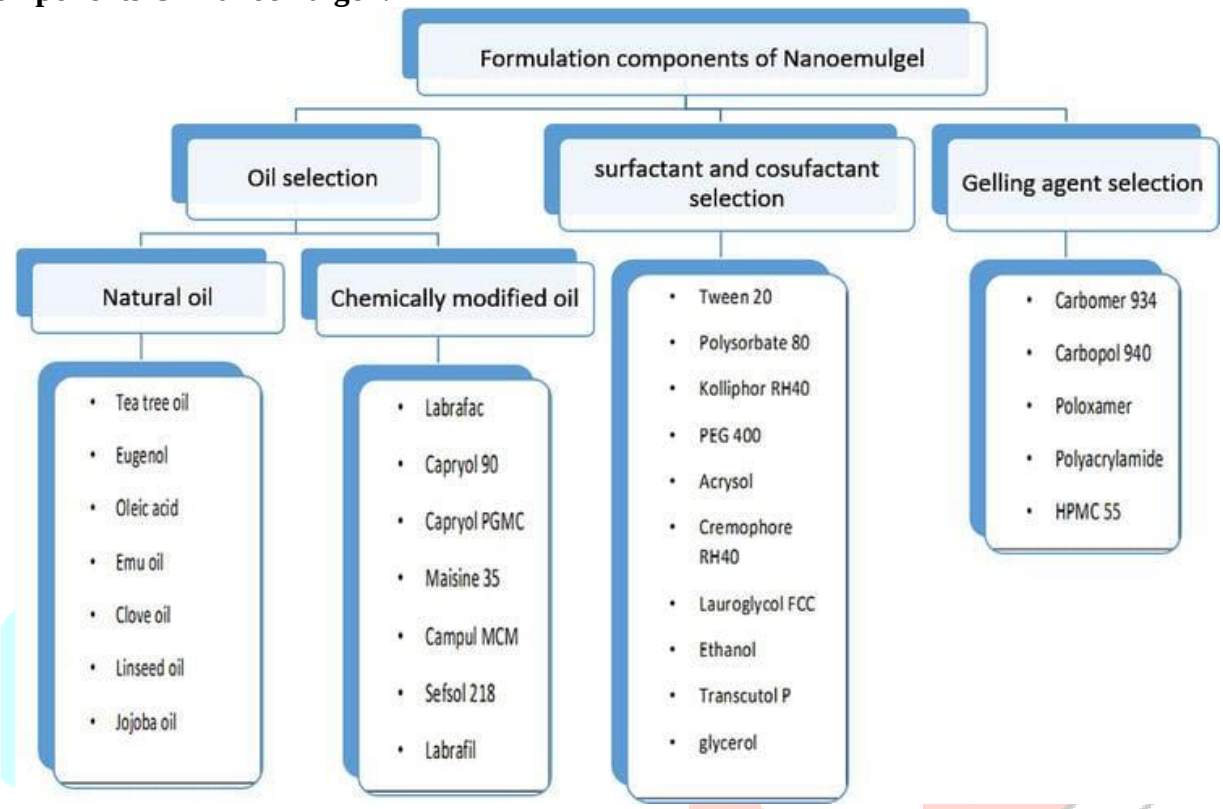

Fig 2 : Schematic representation of formulation component of Nanoemulgel

Nano-emulgels are made up of two individual systems; the gelling agent and the nano-emulsion i.e., emulsion consisting of nano droplets which are of o/w or w/o type. Both emulsion types possess an aqueous and an oily phase. The gel base consists of polymers that can swell on the absorption of a liquid.

3.1.1 Oil Phase

The selection of oil and its quantity depends on the application and utility of the nano-emulgel. The permeability, stability, and viscosity of the prepared nano-emulsion depends on the type and quantity of chosen lipid component, i.e., oil phase. Primarily in case of pharmaceutical and cosmetic applications, the oil phase is made up of either naturally or synthetically originated lipids, unless the oil phase itself is an active ingredient. The consistency of the lipids may vary from liquid to high molecular solids. The hydrophobicity of an oil plays a crucial role in forming a stable emulsion, wherein poor hydrophobicity of the oil is shown to increase the emulsification, concurrently affecting the solubility of lipophilic moieties [7].

For example, oleic acid is frequently used oil in nano-emulgel formulations and is obtained from vegetable and animal sources. It is a biodegradable and biocompatible omega-nine fatty acid and has elevated solubilization characteristics along with improving percutaneous absorption [8].
Antioxidants present in oleic acid contribute to cellular membrane integrity. It also repairs cell damage and showcases formulation stabilization [9].

3.1.2. Surfactant System

Surfactants are an essential ingredient in nano-emulsion, which are utilized in the stabilization of the unstable mix of two immiscible phases. This is achieved by a decreasing the interfacial tension amongst the two phases and alteration of dispersion entropy. The surfactant should show quick adsorption along the interface of the liquids. The final result is a decrease of interfacial tension and inhibition of coalescence of the individual nano-sized droplets [10].

Based on the charge, the surfactants are of four main categories i.e., cationic, non-ionic, anionic, and zwitterionic nature. The surfactants derived from natural sources such as bacteria, fungi, and animals are being considered as a potential option, due to their safety, biodegradability, and biocompatibility. Bio-surfactants show a similar mechanism in decreasing surface tension along the interface due to amphiphilic properties. This is mainly due to the presence of non-polar short fatty acids and polar functionalities as the tail and head respectively.They are more bio-compatible and safer than synthetic surfactants [11].

3.1.3. Co-Surfactant System

Co-surfactants support surfactants during the emulsification of oil in the water phase. Co-surfactants are required for decreasing the interfacial tension and improving the emulsification [12].
Flexibility is added to the interfacial film along with attaining transient negative interfacial tension due to co-surfactants. The association between the surfactant and co-surfactant along with the partitioning of the drug in immiscible phases decides the drug release from the nano-emulgel. Hence co-surfactant selection is equally important as surfactant. The commonly used co-surfactants are PEG- 400, transcutol® HP, absolute ethyl alcohol, and carbitol [13].

3.1.4. Gelling Agents

Gelling agents upon addition to the appropriate media as a colloidal mixture forms a weakly cohesive three-dimensional structural network with a high degree of cross-linking either physically or chemically providing consistency to nano-emulgel.In topical applications, these agents are used to stabilize the formulation, to attain optimum delivery of the drug across the skin. They play an important role in determining various parameters of the formulation like consistency, rheological properties, bio-adhesive properties, pharmacokinetics, spreadability, and extrudability. Based on the origin, these gelling agents are divided into natural, synthetic, and semi-synthetic.[14-16].

3.2.Preparation of Nano-Emulgel :

Nano-emulgel is a non-equilibrium formulation of structured liquids requiring energy, surfactant, or both for its preparation. They are spontaneously formulated by mixing the components. This is undertaken by introducing energy in the biphasic system or decreasing the interfacial tension between the interfaces of the two immiscible phases [17].There are various nano-emulgel preparation methods reported based on the order of mixing of oil and aqueous phase [18].

As illustrated in Figure 3A solubilized the drug in the oil phase and gelling agent in the water phase separately. The oil phase is added to the aqueous gel phase under stirring followed by homogenization to form an emulsion. The sol form of gelling agent in the emulsion is converted to gel by various mechanisms like adding a complexing agent or adjusting to the required pH [19].

As illustrated in Figure 3B divided the total quantity of water required for the preparation into two parts. One part of the divided quantity is used to prepare pre-emulsion and the other part is used for the preparation of gel. Later, these two components are mixed together under stirring [20].

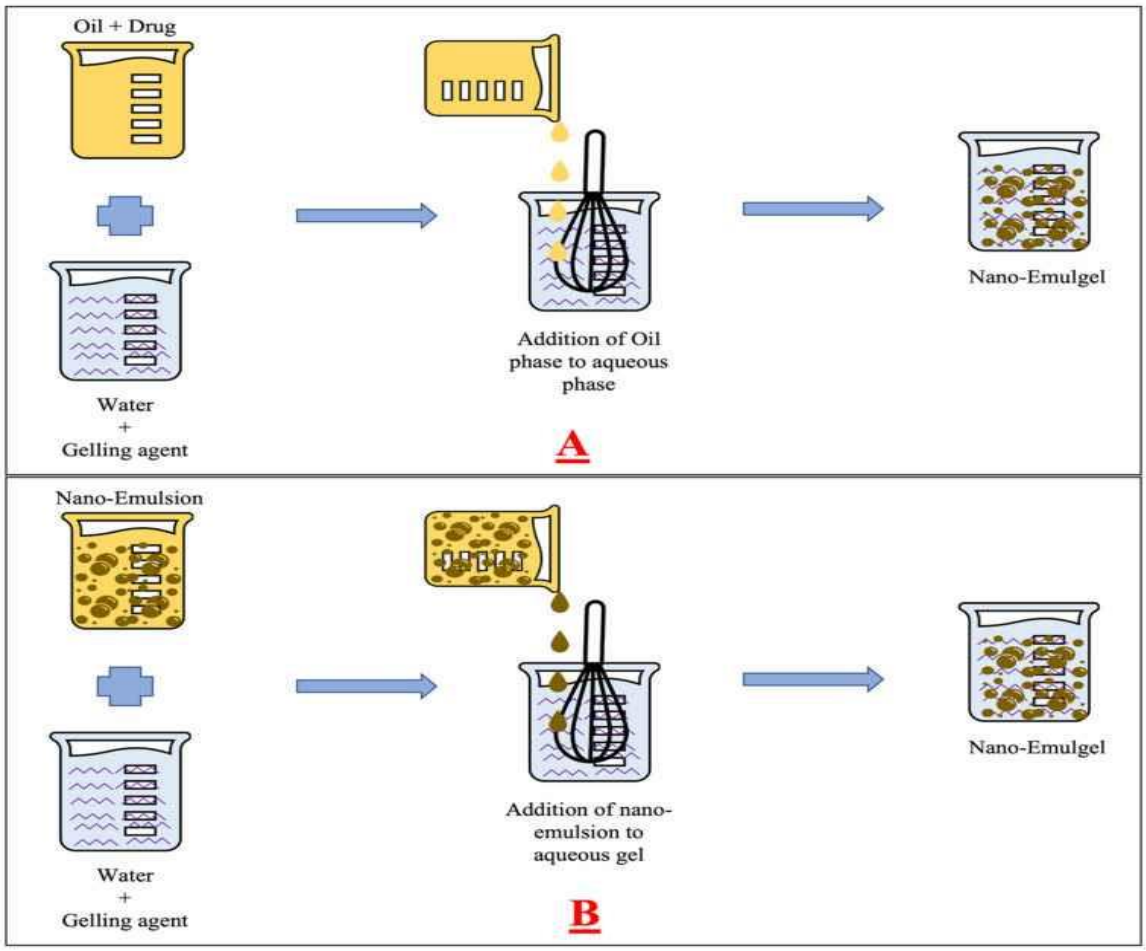

Fig 3: Methods of preparation of Nanoemulgel

Nano-emulgel formulation preparation can be further divided into two types based on the implementation of high-energy and low-energy emulsification techniques. High energy method involves the use of mechanical devices to produce a highly disruptive force in which both phases undergo size reduction. Hence this method may lead to the heating up of components in the formulation causing thermodynamic instability of the formulation and making it not suitable for thermo-labile drugs. Microfluidizers, high-pressure homogenizers, and ultrasonicated are high-energy methods employed to obtain a nanosized emulsion. This method is used for preparing nano-formulation of sizes of about 1 nm.

Phase inversion, self-emulsification, temperature, and phase transition are techniques of low energy approach. These methods provide the required thermodynamic stability to the nano-emulsion. The spontaneous method involves mixing oil, surfactant, and water in the best ratio possible and is most applicable for thermolabile compounds. The emulsification process is based on the surfactant and co-surfactant characteristics and their order of addition. Temperature-based alterations in HLB are utilized for non-ionic surfactants like Tween 20 Tween 60, Tween 80, Labrasol [21].This method is mostly utilized for phase transition during phase inversion. Application of cooling with constant stirring will lead to a reversal of emulsion prepared at inversion temperature. Reduction in phase inversion temperature facilitates the inclusion of thermolabile components using this technique [22].

The second step incorporates gelling agent to change the liquid state to gel in the nano-emulsion. The thixotropic nature of the gelling agent facilitates the gel-solution conversion when shear stress is applied to the preparation keeping the volume constant. This leads to thickening in o/w nano-emulsion because of the creation of a gelled structure.

3.3.Advantages:

1.The ability to resist First-pass metabolism.
2.Effectiveness for a managed and long-term drug delivery system has been proven.
3.Skin friendly.
4.Appropriate for self-medication.
5.Patient accept it quickly.
6.Nanoemulsion provides large surface area and free energy which make an efficient delivery system.
7.Emulsion defect like Creaming, phase separation, flocculation, and coalescence is not found in nanoemulsion.
8.Nanoemulsion prepared in variety of formulations, foams, creams, sprays and much other cosmetic formulation.
9.It is safe on transdermal application due to its non-toxic nature.
10.By using biocompatible surfactant in nanoemulsion formulation, it can be administered orally.
11.It shows better penetration of drug because the nano-sized particles can easily enter by the rough skin surface.
12.By the process of precipitation and interfacial poly-condensation of nanoemulsion, nanocapsule and nanosperes are prepared.

3.4. Disadvantages:

1.Bubbles formed during emulgel formulation.
2.For utilization in pharmaceutical application, surfactant used ought to be non-poisonous.
3.Possibility of allergenic reactions.
4.Skin irritation on contact dermatitis.
[23].

4.CHARACTERIZATION STUDIES OF NANO-EMULGEL

4.1.Zeta Potential:

The particles in a solution usually possess a layer of ions on their surface, referred to as the stern layer. Adjacent to the stern layer, there exists a diffuse layer of loosely bounded ions, which along with the stern layer collectively called an electrical double layer. There is a boundary between the ions in the diffuse layer that move with the particle and the ions that remain with the bulk dispersant. The zeta potential is the electrostatic potential at this “slipping plane” boundary [24].

Zeta potential measurement provides an indirect measure of the net charge and is a tool to compare batch-to-batch consistency. The higher the zeta potential, the greater the repulsion resulting in increased stability of the formulation. For example, the high zeta potential of emulsion globules prevents them from coalescing. A surface charge modifier may also be used to adjust the surface charge. For instance, if a negatively charged surface modifier is used, the zeta-potential value becomes negative, and vice-versa [25,26].

4.2. Droplet Size Measurement and Polydispersity Index (PDI):

The size of globule in nanoemulgel is referred as its hydrodynamic diameter, which is a diameter of equivalent hard sphere that diffuses at the same rate as the active moiety [27]. The PDI determines the distribution of droplet size and is defined as the standard deviation of droplet size divided by mean droplet size. The droplet size and the polydispersity index are closely connected to the stability and drug release, as well as the ex-vivo and in-vivo performance of the dosage form. In addition, it is important to measure consistency between different batches. The globule size and PDI of the formulation can be measured using a zeta sizer or master sizer. The globule size of the emulsion can be determined using the principle of dynamic light scattering, in which the transitional diffusion coefficient is measured by monitoring the interaction between the laser beam and dispersion, as well as the Polydispersity index [28-29].

4.3. Rheological Characterizations:

Rheology is the study of the deformation and flow of materials. The rheological characterization of materials reveals the influence of excipient concentrations like oils, surfactants, and gelling agents on the formulation's viscoelastic flow behavior. If a formulation's viscosity and flow characteristics vary, this may influence its stability, drug release, and other in-vivo parameters. In this instance, the formulation's shear thinning tendency generates a thin layer on the skin surface, improving permeability, whereas a thicker formulation decreases permeation. Therefore, the rheological behavior is an extremely important factor in the formulation of nanoemulgel and several unique types of viscometers can be used to determine the rheological behavior [30].FDA recommends the evaluation of complete flow curves whenever possible, plotted as both heat stress versus shear rate and viscosity versus shear rate across multiple shear rates until low or high plateaus are observed. If a formulation exhibits plastic flow, yield stress values should be evaluated.

4.4. Spreadability Testing:

The spreadability property of the topical dosage form ensures the evenly spreading of the dosage form, thus delivering a stranded dose subsequently affecting the efficacy. The viscosity of the nanoemulgel greatly affects the spreadability property . To date, no standard method has been established for measuring the spreadability of the dosage form. A few tests, that are commonly used for a good approximation of spreadability are a parallel-plate method and human subject assessment etc. The parallel-plate method (slip and drag method) is a widely employed technique because of its simplicity and relatively economic [31] .

The instrumental setup consists of two glass slides of the same length, one of which is stationarily attached to the wooden block, and the other glass slide is mobile attached to a pulley at one end to measure spreadability. Spreadability is determined by the emulgel's 'Slip' and 'Drag' qualities. The nanoemulgel dosage form will be placed on a stationary glass slide, which is then squeezed in between stationary and mobile glass slides. The formulation is squeezed firmly for uniformly spreading formulation between two slides and to remove any air bubbles. The known weights are added to the pulley until the upper slide slips off from the lower slide. The time required for slipping off is recorded, which is used to calculate spreadability using the following equation [32].

$$S = M * L / T$$

where, *S*, *M*, *L* and *T* respectively represent the spreadability, weight bounded to the upper slide, Length of the slide, and Time taken to detach the slides.

4.5. In-Vitro Release Test (IVRT):

The efficacy and safety of the API are associated with drug release from the dosage form. The IVRT serves as a tool for assessing the quality of the drug product [33]. According to FDA, the IVRT studies for semi-solid dosage forms are conducted using either the vertical diffusion cell or an immersion cell. The vertical diffusion cell consists of receptor and donor chambers, separated by a receptor membrane. The donor chamber holds the sample of dosage form, while the receptor chamber holds the receptor media. The receptor media can be a buffer or hydro-alcoholic solution, selected based on the solubility, sink condition, and stability of the API. The skin-like receptor membrane is selected based on the effective pore size, high permeability and expected inertness towards the API. If necessary, the receptor membrane should be saturated with release media. The temperature of the media should be maintained around 32 °C ± 1 °C for topical administering products, for products intended for mucosal membrane the temperature should be 37 °C ± 1 °C. A Teflon-coated magnetic stirrer is used for stirring the receptor media. While the immersion cell model has a cell body, which acts as a reservoir [34].

The cell body is covered with a membrane and closed using a leakproof seal (retaining ring cap) that ensures no leakage of the dosage form. The retaining ring cap possesses an opening on the top, and it should be adjusted in such a way that the membrane is in contact with the dosage form on the bottom and release media on the top. The whole setup is used along with the USP-2 apparatus, wherein the immersion cell is placed in flat bottomed dissolution vessel with a usual volume of 150–200 mL. A mini spin-paddle is used for stirring or agitating the media [35].

4.6. Bio-Adhesive Property:

Bio-adhesive strength is used to determine the force required to detach the drug carrier system from a biological surface. This property is important for a topical dosage form if prolonged contact is required [36].This test is usually performed using rat or pig skin, the latter is preferred because of its resemblance to human skin. There are various techniques to measure this property but none of them is approved by FDA. The texture analyzer is one such technique, where the upper mobile probe and stationary lower base plate will be covered with skin. The dosage form is placed on the skin of the base plate. The upper probe is lowered to contact the lower base plate and the contact is maintained for at least a minute. The upper probe is lifted slowly until the separation of skin sheets. The force required to separate the two skin sheets will be measured by the instrument and represented as the area under the force-distance curve [37].

4.7. pH:

The pH of all the freshly prepared formulations of NE and NEG was determined using digital pH meter initially at 0 h and then over a period of 28 days [38].Fabrication and characterizations of pharmaceutical emulgel Co-loaded with naproxen-eugenol for improved analgesic and anti-inflammatory effects).

4.8.Viscosity measurement:

The viscosity study of the fabricated blank and drug loaded formulations were assessed using viscometer (NDJ, 8S, Korea) at indicated temperatures, i.e. 8 °C, 25 °C and at 40 °C at regular intervals (Day 0, Day 7, Day 14, Day 21 and at Day 28) [39]. Fabrication, in vitro, and in vivo Assessment of eucalyptol-loaded nanoemulgel as a novel paradigm for wound healing). For the operation, spindle no. 4 of viscometer was used for the viscosity determination. The rotation of the spindle was set at 6 rpm and 12 rpm for some minutes and readings were noted.

4.9. FTIR analysis:

Fourier Transform Infrared Spectroscopic (FTIR) analysis was performed for the pure drug, formulation components (Carbopol 940 powder, Tween 80, PEG-400) and developed nanoemulgel. It was analyzed in wave number range of 4000 to 400 cm−1 for each sample.The study was used to check the interaction between the drug and various components of nanoemulgel [40].

5.REFERENCES

1.Chen, H., Khemtong, C., Yang, X., & Chang, X. (2013). Gelling properties of oil-in-water nanoemulsions prepared by phase inversion composition method. Journal of Colloid and Interface Science, 393, 183-190.
2.Zaki, N. M., & Awad, G. A. S. (2014). Nanoemulsion as a transdermal drug delivery system: Formulation,characterization, and application. International Journal of Nanomedicine, 9, 2845-2856.
3.Shadab Md, Nabil A, Alhakamy, Hibah M, Sabna K, Javed A. Improved Analgesic and anti-inflammatory effect of Diclofenac Sodium by Topical Nanoemulgel: Formulation Development – In-vitro and In-vivo studies.Journal of chemistry, 2020.
4.M Rieger, L Lachman, H Lieberman, J Kanig (1986) the Theory and Practice of Industrial Pharmacy. PA Lea and Febiger, Philadelphia 3rd edn. Pp. 502-533.

5.Gao F., Zhang Z., Bu H., Huang Y., Gao Z., Shen J., Zhao C., Li Y. Nanoemulsion Improves the Oral Absorption of Candesartan Cilexetil in Rats: Performance and Mechanism. J. Control. Release. 2011;149: 168–174.
6.Aithal G.C., Narayan R., Nayak U.Y. Nanoemulgel: A Promising Phase in Drug Delivery. Curr. Pharm. Des. 2020;26:279–291.
7.Vandamme T.F. Microemulsions as Ocular Drug Delivery Systems: Recent Developments and Future Challenges. Prog. Retin. Eye Res. 2002;21: 15–34.
8.Williams A.C., Barry B.W. Penetration Enhancers. Adv. Drug Deliv. Rev. 2012;64:128–137.
9.Aggarwal G., Dhawan B., Harikumar S. Enhanced Transdermal Permeability of Piroxicam through Novel Nanoemulgel Formulation. Int. J. Pharm. Investig. 2014; 4:65.
10.Silva H.D., Cerqueira M.A., Vicente A.A. Influence of Surfactant and Processing Conditions in the Stability of Oil-in-Water Nanoemulsions. J. Food Eng. 2015;167:89–98.
11.Hu J., Chen D., Jiang R., Tan Q., Zhu B., Zhang J. Improved Absorption and in Vivo Kinetic Characteristics of Nanoemulsions Containing Evodiamine–Phospholipid Nanocomplex. Int. J. Nanomed. 2014;9: 4411–4420.
12.Poré J. Emulsions, Micro-Émulsions, Émulsions Multiples. Editions Techniques des Industries des Corps Gras; Neuilly sur Seine, France: 1992.
13.Wang Z., Mu H.-J., Zhang X.-M., Ma P.-K., Lian S.-N., Zhang F.-P., Chu S.-Y., Zhang W.-W., Wang A.-P., Wang W.-Y., et al. Lower Irritation Microemulsion-Based Rotigotine Gel: Formulation Optimization and in Vitro and in Vivo Studies. Int. J. Nanomed. 2015;10. 633–644.
14.Shah H., Jain A., Laghate G., Prabhudesai D. Remington. Academic Press; Cambridge, MA, USA: 2021. Pharmaceutical Excipients; pp. 633–643.
15.Ojha B., Jain V.K., Gupta S., Talegaonkar S., Jain K. Nanoemulgel: A Promising Novel Formulation for Treatment of Skin Ailments. Polym. Bull. 2021;79 : 1–25
16.Dubey S.K., Alexander A., Sivaram M., Agrawal M., Singhvi G., Sharma S., Dayaramani R. Uncovering the Diversification of Tissue Engineering on the Emergent Areas of Stem Cells, Nanotechnology and Biomaterials. Curr. Stem Cell Res. Ther. 2020;15: 187–201.
17.Anton N., Vandamme T.F. The Universality of Low-Energy Nano-Emulsification. Int. J. Pharm. 2009;377: 142–147.
18.Sharma V., Nayak S.K., Paul S.R., Choudhary B., Ray S.S., Pal K. Polymeric Gels. Woodhead Publishing; Sawston, UK: 2018. Emulgels; pp. 251–264.
19.Lupi F.R., Gabriele D., Seta L., Baldino N., de Cindio B., Marino R. Rheological Investigation of Pectin-Based Emulsion Gels for Pharmaceutical and Cosmetic Uses. Rheol. Acta. 2015;54 :41–52.
20.Dong L., Liu C., Cun D., Fang L. The Effect of Rheological Behavior and Microstructure of the Emulgels on the Release and Permeation Profiles of Terpinen-4-Ol. Eur. J. Pharm. Sci. 2015;78: 140–150.
21.Solè I., Pey C.M., Maestro A., González C., Porras M., Solans C., Gutiérrez J.M. Nano-Emulsions Prepared by the Phase Inversion Composition Method: Preparation Variables and Scale Up. J. Colloid Interface Sci. 2010;344: 417–423
22.Lovelyn C., Attama A.A., Lovelyn C., Attama A.A. Current State of Nanoemulsions in Drug Delivery. J. Biomater. Nanobiotechnol. 2011;2: 626–639
23.Panwar, N Upadhyay, M Bairagi, S Gujar, G Darwhekar (2011) Emulgel: A Review. Asian Journal of Pharmacy and Life Science 1(3): 333-343.
24. Clogston J.D., Patri A.K. Zeta Potential Measurement. Methods Mol. Biol. 2011;697: 63–70.
25.Krishna K.V., Saha R.N., Dubey S.K. Biophysical, Biochemical, and Behavioral Implications of ApoE3 Conjugated Donepezil Nanomedicine in a Aβ1-42Induced Alzheimer's Disease Rat Model. ACS Chem. Neurosci. 2020;11: 4139–4151.
26.Khosa A., Krishna K.V., Saha R.N., Dubey S.K., Reddi S. A Simplified and Sensitive Validated RP-HPLC Method for Determination of Temozolomide in Rat Plasma and Its Application to a Pharmacokinetic Study. J. Liq. Chromatogram. Relat. Technol. 2018;41: 692–697.
27.Manus Maguire C., Rösslein M., Wick P., Prina-Mello A. Characterisation of Particles in Solution–a Perspective on Light Scattering and Comparative Technologies. Taylor Fr. 2018;19: 732–745.
28.Sneha K., Kumar A. Nanoemulsions: Techniques for the Preparation and the Recent Advances in Their Food Applications. Innov. Food Sci. Emerg. Technol. 2022;76: 102914
29.Khosa A., Krishna K.V., Dubey S.K., Saha R.N. Lipid Nanocarriers for Enhanced Delivery of Temozolomide to the Brain. Methods Mol. Biol. 2020;2059: 285–298.

30.Anand K., Ray S., Rahman M., Shaharyar A., Bhowmik R., Bera R., Karmakar S. Nano-Emulgel: Emerging as a Smarter Topical Lipidic Emulsion-Based Nanocarrier for Skin Healthcare Applications. Recent Pat. Antiinfect. Drug Discov. 2019;14: 16–35.
31.Garg A., Aggarwal D., Garg S., America A.S.-T.N. Spreading of Semisolid Formulations: An Update. Pharm. Technol. N. Am. 2002;26: 84.
32.Nikumbh K.V., Sevankar S.G., Patil M.P. Formulation Development, in Vitro and in Vivo Evaluation of Microemulsion-Based Gel Loaded with Ketoprofen. Drug Deliv. 2015;22: 509–515.
33.Shah V.P., Simona Miron D., Ștefan Rădulescu F., Cardot J.M., Maibach H.I. In Vitro Release Test (IVRT): Principles and Applications. Int. J. Pharm. 2022;626: 122159
34.Sheshala R., Anuar N.K., Abu Samah N.H., Wong T.W. In Vitro Drug Dissolution/Permeation Testing of Nanocarriers for Skin Application: A Comprehensive Review. AAPS PharmSciTech. 2019;20: 164.
35.Kanfer I., Rath S., Purazi P., Mudyahoto N.A. In Vitro Release Testing of Semi-Solid Dosage Forms. Dissolut. Technol. 2017;24:52–60.
36.Shaikh R., Raj Singh T., Garland M., Woolfson A., Donnelly R. Mucoadhesive Drug Delivery Systems. J. Pharm. Bioallied Sci. 2011;3:89–100.
37.Amorós-Galicia L., Nardi-Ricart A., Verdugo-González C., Arroyo-García C.M., García-Montoya E., Pérez-Lozano P., Suñé-Negre J.M., Suñé-Pou M. Development of a Standardized Method for Measuring Bioadhesion and Mucoadhesion That Is Applicable to Various Pharmaceutical Dosage Forms. Pharmaceutics. 2022;14: 1995.
38.B.A. Khan, S. Ahmad, M.K. Khan, K.M. Hosny, D.M. Bukhary, H. Iqbal, S.S. Murshid, A.A. Halwani, M. Alissa, F. Menaa Fabrication and characterizations of pharmaceutical emulgel Co-loaded with naproxen-eugenol for improved analgesic and anti-inflammatory effects.Gels 2022. 8(10), 608;1-6.
39.Rehman et al., 2022 A. Rehman, M. Iqbal, B.A. Khan, M.K. Khan, B. Huwaimel, S. Alshehri, A.H. Alamri, R.M. Alzhrani, D.M. Bukhary, A.Y. Safhi, K.M. Hosny. Fabrication, in vitro, and in vivo Assessment of eucalyptol-loaded nanoemulgel as a novel paradigm for wound healing.Pharmaceutics 2022, 14(9), 1971.
40Haider, B.A. Khan, M.K. Khan Formulation and evaluation of topical linezolid nanoemulsion for open incision wound in diabetic animal model. 2022 Apr 28;23(5):129.